# PROCESS FOR PREPARING CROSS-BRIDGED TETRAAZA MACROCYCLES

## FIELD OF THE INVENTION

The present invention relates to an improved process for preparing cross-bridged tetraaza macrocycles, said macrocycles suitable as ligands for use in preparing transition metal complexes. The present invention provides a process which is well suited for use in industrial and other commercial preparations of the herein described crossed-bridged macrocycles.

## BACKGROUND OF THE INVENTION

Tetraaza macrocyclics, for example, cyclam, have been prepared in numerous ways, however, there is a paucity of information relating to the preparation of cross-bridged tetraaza macrocyclics *inter alia* bis N-substituted tetraaza macrocyclics *inter alia* 5,12 dialkyl 1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecanes which have recently found wide applicability as ligands especially in the area of transition metal catalysts *inter alia* bleach catalysts.

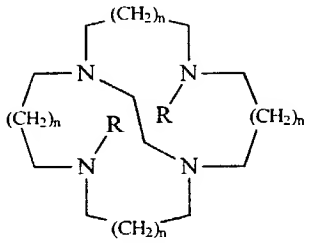
WO 98/39335 A1 "Improved Methods of Making Cross-Bridged Macropoly-cycles" discloses a rational procedure for preparing cross bridged macropolycyclic ligands which is amenable to high yields necessary for industrial scale-up. However, the reductive ring cleavage step which results in bicyclo bridged-ring formation utilizes a borohydride reducing agent. This type of reducing agent can place constraints on the formulator. For example, the need to break up the amine/borohydride complex during work-up and the proper recovery and disposal of boron waste products adds cost to the process. Also, if excess borohydride is needed, this requires neutralization which involves the use of acid and the evolution of large quantities of hydrogen gas.

Therefore, a need exists for a highly quantitative, preferably catalytic, process for preparing cross-bridged macropolycyclic ligands which is adaptable to either continuous flow processes or batch preparations.

## SUMMARY OF THE INVENTION

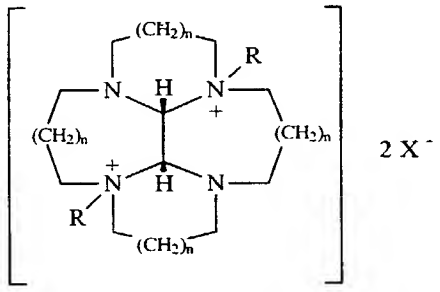
The present invention meets the aforementioned needs in that it has been surprisingly discovered that select bis N-substituted tetraaza macrocyclics can be converted to cross-bridged macropolycyclic ligands via catalytic hydrogenation.

A first aspect of the present invention relates to a process for preparing a tetraaza macrocyclic ligand having the formula:



wherein each R is independently $C_1$-$C_8$ linear or branched alkyl, $-(CH_2)_xCO_2M$, and mixtures thereof, preferably both of the R units are not methyl; M is hydrogen or a salt forming cation; x is from 1 to 6; each index n is independently from 0 to 3; said process comprising the steps of:

a) hydrogenating a tetraaza macrocyclic ligand precursor having the formula:



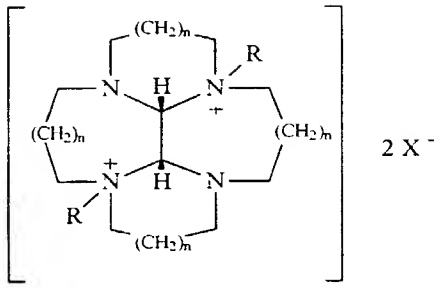
wherein $X^-$ is an anion which provides charge neutrality, with from about 1 ppm of a transition metal hydrogenation catalyst at a pH of at least 8 to form a tetraaza macrocyclic ligand; and

b) optionally isolating said ligand.

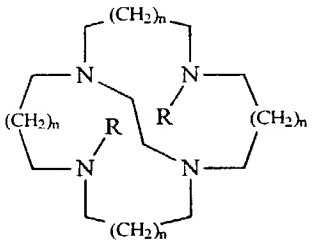
These and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius ($^o$ C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the catalytic hydrogenation of tetraaza macrocycles having the formula:

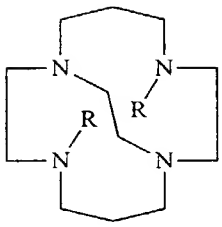



wherein the covalent bond between the N-substituted quaternary ring nitrogen and the bridging carbon is broken and a cross-bridged macrocyclic ligand having the formula:




is the resulting product.

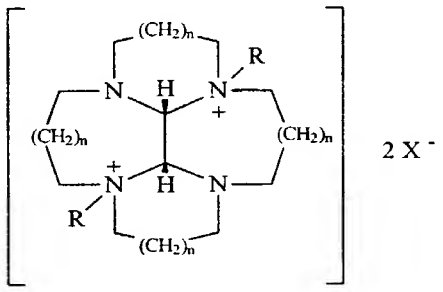
In the above formula each R is independently $C_1$-$C_8$ linear or branched alkyl, -$(CH_2)_xCO_2M$, and mixtures thereof, preferably both of the R units are not methyl; more preferably one R unit is methyl and the other R unit is selected from the group consisting of ethyl, propyl, butyl, pentyl, hexyl, and mixtures thereof; of the methyl/alkyl R unit mixtures preferably one R is methyl and the other R is ethyl or propyl. A most preferred ligand consists of a unit wherein one R unit is methyl and the other R unit is ethyl. A preferred ligand is a macrocyclic ring wherein each R unit is ethyl. M is hydrogen or a salt forming cation, non-limiting examples of which are sodium, potassium, calcium, ammonium. When R is -$(CH_2)_xCO_2M$ the index x has the value from 1 to about 6, preferably x is 1. The index n defines the size of the macrocyclic ring. The index n has the value of from 0 to about 3. A preferred macrocyclic ring has one opposite set of n indices equal to 1 and the other set of n indices equal to 0 as in the general formula:



wherein R is the same as defined herein above.

Preferred ligands according to the present invention comprise R unit pairs which are selected from the group consisting of methyl and ethyl, diethyl, methyl and propyl, ethyl and propyl, methyl and butyl, ethyl and butyl, and mixtures thereof.

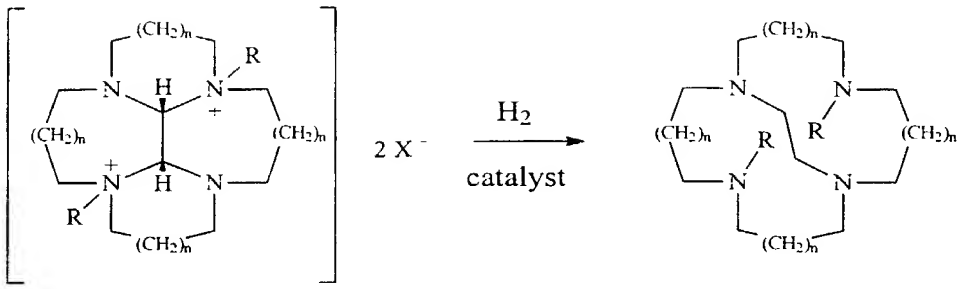
The starting materials for the process of the present invention are tetraaza macrocyclic ligand precursors, or alternatively, bis-quaternary *cis* tetracycles, having the formula:



wherein R and n are the same as defined herein above. X is an anion which serves to provide electronic neutrality to the bis-quaternary *cis* tetracycle. Those of ordinary skill in the art recognize that the term "electronic neutrality" refers to "a sufficient amount of an anionic species which satisfies the molecular charge balance requirements" and that a mixture of mono-, di-, tri-, etc. electronic species may be use herein. X preferably has unit negative charge, for example, halogen, tosylate, methylsulfate, ethylsulfate. However, X may have more than one negative charge, for example, sulfate, in which case the formulator requires only half the amount necessary when using a unit negative-charged anion. Preferred X is chloride, bromide, iodide, sulfate, ethyl sulfate, methyl sulfate, tosylate, mesylate, triflate, and mixtures thereof.

STEP (a) Hydrogenation - Reductive Cleavage

Step (a) comprises the reductive cleavage via catalytic hydrogenation as outlined in the following scheme:




wherein the *cis*-tetracycle bis quaternary salt is converted to the cross-bridged tetraaza macrocycle.

Step (a) is conducted in the presence of a catalyst, preferably a supported catalyst. Non-limiting examples of catalysts include platinum on carbon, palladium on carbon (Pd/C), palladium hydroxide on carbon ($Pd(OH)_2/C$), rhodium on carbon (Rh/C), Raney nickel, and mixtures thereof. A preferred catalyst is $Pd(OH)_2/C$. The supported catalysts may comprise from about 1% to about 50% by weight of transition metal, however, the pure metal, i.e. palladium, can be used without the need for a "support", i.e., carbon. A "catalytic amount" of catalyst is sufficient to provide the reduction of step (a). For the purposes of the present invention the term catalytic amount is defined as "from about 1 ppm of a 5% by weight transition metal catalyst". However, the formulator, due to poisoning of the catalyst surface by reaction products may use more than a catalytic amount of a catalyst. The amount of catalyst used in step (a) of the present invention is preferably from about 10 ppm of a catalyst which contains from about 5% to 50% by weight, of a transition metal, more preferably from about 100 ppm, yet more preferably from about 0.1% by weight, of a transition metal supported catalyst. A reaction solution which comprises 0.1% by weight, of a transition metal supported catalyst, said catalyst comprising, for example, 10% by weight of palladium on carbon, has 0.01% transition metal or 100 ppm transition metal present.

The amount of hydrogen gas present in step (a) of the present invention need only be enough to sufficiently saturate the catalyst surface, preferably the hydrogen pressure is from 200 psi, more preferably from 400 psi, most preferably from 800 psi to about 2000 psi, more preferably to 1000 psi.

Step (a) of the present process can be conducted at a temperature of from 20° C, preferably from about 40° C, more preferably from about 60° C to about 100° C, preferably to about 90° C, more preferably to about 80° C, most preferably to about 65° C.

The pH under which Step (a) must be conducted is at least 8, preferably at least 10, more preferably at least about 11. Preferably the base which is used to adjust the pH is in the form of an aqueous solution. Preferred bases are selected from the group consisting of potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, and mixtures thereof. As a non-limiting example, it is satisfactory to use a sufficient amount of 1 M (molar) aqueous base to adjust the pH to the required level. A convenient and preferred base is potassium carbonate.

As a suitable alternative, Step (a) can be conducted in the presence of a solvent other than water, or in the absence of water. A mixture of a suitable solvent and water is a suitable means for conducting the hydrogenation process of the present invention. In the case where water is absent, sufficient base must be present to stabilize the transition state of the reactants and products during hydrogenation. Non-limiting examples of solvents include methanol, ethanol, n-propanol, isopropanol, N,N-dimethyl formamide, n-butanol, iso-butanol, tert-butanol, and mixtures thereof; preferred solvents are selected from the group consisting of ethanol, n-propanol, N,N-dimethyl formamide, and mixtures thereof. When a solvent is present and the base is in the form of an aqueous solution, the ratio of said volume of an aqueous base, to said solvent is from about 1:10 to about 1:1, preferably the ratio of the volume of aqueous base to solvent is 1:4. It is desirable, but not a requirement, that the aqueous base and solvent form a two phase system.

The process of the present invention comprises an optional, although preferred, Step (b) which is an isolation step. Typically this step involves filtration of the reaction solution to remove the catalyst. In addition, this step may comprise a neutralization step, however, the product can be isolated or removed from the reaction matrix in any manner which the formulator desires.

When filtration of the catalyst is a desired step, the reaction solution containing the cross-bridged ligand is filtered to remove the catalyst to form a crude filtrate. This crude filtrate can be neutralized or the tetraaza macrocyclic ligand can be isolated by extraction or crystallization directly from the preferably aqueous solution.

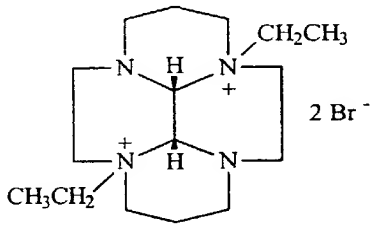
Steps (a) and (b) and any optional extensions thereto, for example, a crystallization step, a solvent drying step, a purging step, may be suitably adapted for either batch processes or continuous processes, for example, continuous flow processes. As mentioned herein, the process of the present invention may comprise other optional steps as deemed necessary and/or desirable by the formulator. These optional steps may include but are not limited to, pre-saturation of the catalyst with hydrogen, drawing a vacuum on the system, and recovery of the catalyst and solvents.

Preferably the ligands formed by the process of the present invention are converted into manganese containing transition metal catalysts in a subsequent, however optional, process step. The bleach catalysts comprise a central manganese atom and a cross-branched ligand formed by the process of the present invention. The final bleach catalyst may comprise one or more other compatible ligands *inter alia* chlorine atom. The preferred catalysts are suitable as bleaching agents.

The following is a non-limiting example of the process of the present invention.

Preparation of **5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane**

To a thick walled, glass autoclave sleeve is added the bis-quaternary *cis* tetracycle having the formula:




(3.0 g, 6.8 mmol) and a 1M aqueous solution of $K_2CO_3$ (30 mL). The solution is agitated to dissolve the substrate then 20% $Pd(OH)_2$/carbon (0.7 g, 1.0 mmol) is added. The glass sleeve is placed into a rocking autoclave and hydrogenated at 65° C with 1900 psig hydrogen for 4 hours. The reaction is cooled and the solution filtered through glass fiber filter paper to remove the catalyst and the filtrate is reduced to a white solid under vacuum. The white solid is suspended in refluxing ethanol and the un-dissolved inorganic salts are collected by filtration. After concentrating the filtrate under vacuum, the resulting oily residue is dissolved in aqueous 4M KOH (4 mL) and extracted three times with 25 mL portions of toluene. The toluene extracts are combined and concentrated *in vacuo* to afford 5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane (1.56 g) in 81% yield as a clear oil.

The following is an example of an optional, but preferred step of the process of the present invention which is conversion to a manganese transition metal bleach catalyst.

Preparation of dichloro **5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane manganese**

To a 100 mL reaction flask is charged anhydrous acetonitrile (50 mL) and 5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane (1.4 g, 5 mmol). The resulting suspension is degassed under vacuum with subsequent re-filling with argon. This process is repeated six times. Manganese(II) chloride (0.590 g, 4.7 mmol) is added and the reaction is refluxed for 3 hours.

The resulting solution is filtered through glass-fiber filter paper. The resulting filtrate is concentrated under reduced pressure at 45° C to afford a solid. The solid is suspended in toluene (50 mL) and the resulting dark supernatant is discarded. Treatment with toluene is repeated five times. The resulting solid is dried under vacuum to yield dichloro 5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane manganese (1.48 g, 73% yield).